chemokine to said receptor. Support for this amendment can be found throughout the Specification, for example, at page 12, line 25 through page 13, line 2.

Claims 1, 45 and 52 have also been amended to recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor. Support for this amendment can be found throughout the Specification, for example, at page 14, lines 27-30.

Claim 5 has been amended to depend upon Claim 1 and to recite proper antecedent basis.

Claim 6 has been amended to more clearly indicate that the antibody recited in parts (b) and (d), as amended, has the epitopic specificity of monoclonal antibodies 1D9 and 8G2, respectively.

Claim 8 has been amended to depend upon Claim 1.

New Claims 53-106 have been added.

Support for new Claims 53-56 can be found throughout the Specification, for example, at page 46, line 22, through page 47, line 25.

Support for new Claims 57, 74, 91 and 99 can be found throughout the Specification, for example, at page 15, lines 22-23.

Support for new Claims 58, 75, 92 and 100 can be found throughout the Specification, for example, at page 17, lines 21-26.

Support for new Claims 59, 76, 93 and 101 can be found throughout the Specification, for example, at page 17, lines 10-20.

Support for new Claims 60, 77, 94 and 102 can be found throughout the Specification, for example, at page 17, lines 21-26.

Support for new Claims 61, 78, 95 and 103 can be found throughout the Specification, for example, at page 18, lines 28-31.

Support for new Claims 62-66 and 81-85 can be found throughout the Specification, for example, at page 19, line 8, through page 20, line 12.

Support for new Claims 67, 68, 86 and 90 can be found throughout the Specification, for example, at page 20, lines 13-15.

Support for new Claims 69, 72, 73, 79, 80, 87 and 104 can be found throughout the Specification, for example, at page 14, lines 4-15 and page 52, lines 27-30.

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Support for new Claims 70, 88, 98, 105 and 106 can be found throughout the Specification, for example, at page 4, lines 2-8.

Support for new Claims 71, 89 and 103 can be found throughout the Specification, for example, at page 4, lines 2-8.

Support for new Claims 96 and 97 can be found throughout the Specification, for example, in Figure 6A.

Support for new Claims 60, 77, 94 and 102 can be found throughout the Specification, for example, at page 17, lines 21-26.

Information Disclosure Statement

A Fourth Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS and consideration of the cited references are respectfully requested.

Declaration Under 37 C.F.R. §1.806 and §1.808

Applicant is submitting concurrently herewith a Declaration Under 37 C.F.R. §1.806 and §1.808 which states that the 1D9 and 8G2 hybridomas referenced in the subject application have been accepted for deposit under the Budapest Treaty and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent. Applicant also notes that the Specification provides the accession numbers, date of deposit, name and address of the depository, and taxonomic description of the deposited biological material (see, for example, page 15, lines 10-21). Thus, Applicant believes that the requirements of 35 U.S.C. §112, first paragraph, have been met.

Rejection of Claims 1-8 and 45-52 Under 35 U.S.C. §102(e)

Claims 1-8 and 45-52 are rejected under 35 U.S.C. §102(e) as being anticipated by Lind *et al.* (U.S. Patent No. 6,084,075; Reference A and AC). The Examiner states that the cited patent meets the broad limitations of the claims, which are directed to a product. The Examiner further states that the product disclosed by Lind *et al.* appears to be identical to or so similar that

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it is indistinguishable from the product claimed by Applicant, and that the disclosure of Lind *et al.* anticipates the claimed invention.

Applicants note that Claims 2, 3, 4 and 7 have been cancelled. Claims 1, 45 and 52 have been amended to recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Lind *et al.* discloses antibodies which bind to CCR2. Some of the antibodies disclosed by Lind *et al.* (antibodies MCPR-03, MCPR-04, MCPR-05 and MCPR-06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table III (col. 14), Lind *et al.* states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52, as amended, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2.

The rest of the antibodies disclosed by Lind *et al.* (MCPR-01 and MCPR-02) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. In Table III (col. 14), Lind *et al.* states that these antibodies recognize amino acids 24-38 of CCR2. Table III also provides a summary of the activities of MCPR-01 and MCPR-02. MCPR-01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table III). MCPR-02 is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table III). That is, MCPR-01 is disclosed as having no effect on the functions assessed, and MCPR-02 is disclosed as stimulating function (e.g., chemotaxis and calcium influx) associated with binding of chemokine to CCR2 (col. 12, lines 32-40, and Figure 4B). Thus, none of the antibodies disclosed by Lind *et al.* anticipate the invention of Claims 1, 5, 6, 8, 45 and 52, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of the chemokine to said receptor. With respect to Claims 46-51, Lind *et al.* provides no teaching or suggestion of an antibody having the particular recited IC_{50} or binding affinity values. Thus, Applicant respectfully believes that Claims 1, 5, 6, 8 and 45-52, as amended, are not

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anticipated by the disclosure of Lind *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-8 and 45-52 Under 35 U.S.C. §102(a)

Claims 1-8 and 45-52 are rejected under 35 U.S.C. §102(a) as being clearly anticipated by Frade *et al.* (*J. Clin. Invest. 100*(3):497-502 (1997); Reference AX; hereinafter "Frade 1"). The Examiner states that Frade 1 discloses an antibody raised against CCR2 which appears to be identical to or so similar that it is indistinguishable from the product claimed by Applicant, and that the disclosure of Frade 1 anticipates the claimed invention.

Applicants note that Claims 2, 3, 4 and 7 have been cancelled. Claims 1, 45 and 52 have been amended to recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Frade 1 discloses the early results of the work which is the basis for the Frade *et al.* reference (*J. Immunology 159*(11):5576-5584 (1997); Reference AW; hereinafter "Frade 2") discussed below. It is clear that Frade 1 pre-dates Frade 2 from two facts. First, Frade 1 was received for publication on January 28, 1997, while Frade 2 was received for publication on June 13, 1997. Second, Frade 2 cites Frade 1 in its list of references (reference 33).

Frade 1 discloses the production and characterization of several anti-CCR2 antibodies. Some of the antibodies are disclosed as specific for the third extracellular domain (amino acids 273-292), and MCP-1R05 is described as being illustrative of this group of antibodies (page 498, col. 2, lines 38-42). These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52, as amended, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2.

Frade 1 also discloses antibodies which are described as specific for the amino-terminal domain (amino acids 24-38), and MCP-1R02 is described as being illustrative of this group of antibodies (page 498, col. 2, lines 38-42). However, the teachings of Frade 1 are misleading with respect to the nature of the effects of the MCP-1R02 antibody.

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Frade 1 states that MCP-1-induced calcium influx and monocyte chemotactic response is blocked by the two CCR2B receptor amino-terminal domain-specific antibodies MCP-1R01 and MCP-1R02 (page 498, col. 2, line 62, through page 499, col. 1, line 8). However, these results could be due either to actual antagonistic activity of the antibodies or to receptor desensitization due to agonist activity of the antibodies. The nature of the effects of the MCP-1R01 and MCP-1R02 antibodies is clarified in Frade 2, which discloses that upon further study it was determined that stimulation of Fluo-3-loaded Mono Mac 1 cells with MCP-1R02 induces a rapid and transient rise in calcium concentration and transmigration, desensitizing the receptor to MCP-1 (pages 5578, col. 2, line 36, through page 5579, col. 1, line 3). Additionally, Frade 2 discloses that antibody MCP-1R01 has neither agonistic nor antagonistic activity with respect to MCP-1-induced calcium influx and transmigration (Table I of Frade 2).

Thus, an accurate statement of the functional effects of the anti-CCR2 antibodies disclosed as specific for the amino-terminal domain of CCR2 requires consideration of the teachings of both Frade 1 and Frade 2. The effects can be summarized as follows: MCP-1R01 has no effect on the functions assessed, and MCP-1R02 stimulates function (e.g., chemotaxis and calcium influx) associated with binding of chemokine to CCR2. Thus, these antibodies do not anticipate the antibodies recited in Claims 1, 5, 6, 8, 45 and 52, particularly in that none of the antibodies inhibits binding of a chemokine to CCR2 and inhibits one or more functions associated with binding of the chemokine to the receptor. With respect to Claims 46-51, Frade 2 provides no teaching or suggestion of an antibody having the particular recited IC_{50} or binding affinity values. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-8 and 45-52 Under 35 U.S.C. §102(a)

Claims 1-8 and 45-52 are rejected under 35 U.S.C. §102(a) as being anticipated by Frade *et al.* (*J. Immunology 159*(11):5576-5584 (1997); Reference AW; hereinafter "Frade 2"). The Examiner states that Frade 2 discloses an antibody raised against CCR2 which appears to be identical to or so similar that it is indistinguishable from the product claimed by Applicant, and that the disclosure of Frade 2 anticipates the claimed invention.

Applicants note that Claims 2, 3, 4 and 7 have been cancelled. Claims 1, 45 and 52 have been amended to recite the phrase "wherein said antibody or antigen-binding fragment thereof

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inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Frade 2 discloses some of the same subject matter as U.S. Patent No. 6,084,075 to Lind *et al.* (Reference A and AC) discussed above. Specifically, Frade 2 discloses antibodies which bind to CCR2. Some of the antibodies disclosed by Frade 2 (antibodies MCP-1R03, MCP-1R04, MCP-1R05 and MCP-1R06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table I, at page 5578, Frade 2 states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52, as amended, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2.

The rest of the antibodies disclosed by Frade 2 (MCP-1R01 and MCP-1R02) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. In Table I, at page 5578, Frade 2 states that these antibodies recognize amino acids 24-38 of CCR2. Table I also provides a summary of the activities of MCP-1R01 and MCP-1R02. MCP-1R01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table I). MCP-1R02 is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table I). That is, MCP-1R01 is disclosed as having no effect on the functions assessed, and MCP-1R02 is disclosed as stimulating function (e.g., chemotaxis and calcium influx) associated with binding of chemokine to CCR2 (page 5578, col. 2, line 42, through page 5579, col. 1, line 3). Thus, none of the antibodies disclosed by Frade 2 anticipate the invention of Claims 1, 5, 6, 8, 45 and 52, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions associated with binding of the chemokine to said receptor.

With respect to Claims 46-51, Frade 2 provides no teaching or suggestion of an antibody having the particular recited IC_{50} or binding affinity values. In fact, Frade 2 states that elevated mAb concentrations (a 100-fold molar excess) are required for complete blockage of MCP-1 activity. Thus, Applicant respectfully believes that Claims 1, 5, 6, 8 and 45-52, as amended, are not anticipated by the disclosure of Frade 2. Reconsideration and withdrawal of the rejection are respectfully requested.

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Rejection of Claims 1-8 and 45-52 Under 35 U.S.C. §102(a)

Claims 1-8 and 45-52 are rejected under 35 U.S.C. §102(a) as being anticipated by Lind *et al.* (WO 97/31949; Reference AL). The Examiner states that the disclosure of Lind *et al.* meets the broad limitations of the claims. The Examiner further states that Lind *et al.* disclose a product which appears to be identical to or so similar that it is indistinguishable from the product claimed by Applicant, and that the disclosure of Lind *et al.* anticipates the claimed invention.

Applicants note that Claims 2, 3, 4 and 7 have been cancelled. Claims 1, 45 and 52 have been amended to recite the phrase "wherein said antibody or antigen-binding fragment thereof inhibits binding of a chemokine to said receptor and inhibits one or more functions associated with binding of the chemokine to said receptor, and wherein said antibody or antigen-binding fragment thereof binds the amino-terminal domain of said receptor."

Lind *et al.* discloses antibodies which bind to CCR2. Some of the antibodies disclosed by Lind *et al.* (antibodies MCPR-03, MCPR-04, MCPR-05 and MCPR-06) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the third extracellular loop (amino acids 273-292) of CCR2. In Table III (page 25), Lind *et al.* states that these antibodies recognize amino acids 273-292 of CCR2. These antibodies plainly do not anticipate Claims 1, 5, 6, 8, 45 and 52, as amended, which recite that the antibody or antigen-binding fragment thereof binds the amino-terminal domain of CCR2.

The rest of the antibodies disclosed by Lind *et al.* (MCPR-01 and MCPR-02) were derived from mice immunized with KLH-coupled synthetic peptides corresponding to the amino-terminal domain (amino acids 24-38) of CCR2. In Table III (page 25), Lind *et al.* states that these antibodies recognize amino acids 24-38 of CCR2. Table III also provides a summary of the activities of MCPR-01 and MCPR-02. MCPR-01 is disclosed as being neither an agonist nor an antagonist of MCP-1-induced calcium influx or transmigration (Table III). MCPR-02 is disclosed as being an agonist of MCP-1-induced calcium influx and transmigration (Table III). That is, MCPR-01 is disclosed as having no effect on the functions assessed, and MCPR-02 is disclosed as stimulating function (e.g., chemotaxis and calcium influx) associated with binding of chemokine to CCR2 (page 20, line 30, through page 21, line 3, and Figure 4B). Thus, none of the antibodies disclosed by Lind *et al.* anticipate the invention of Claims 1, 5, 6, 8, 45 and 52, which recite that the antibody or antigen-binding fragment thereof inhibits one or more functions

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associated with binding of the chemokine to said receptor. With respect to Claims 46-51, Lind *et al.* provides no teaching or suggestion of an antibody having the particular recited IC_{50} or binding affinity values. Thus, Applicant respectfully believes that Claims 1, 5, 6, 8 and 45-52, as amended, are not anticipated by the disclosure of Lind *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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